

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

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Applicant's or agent's file reference ON/4-32823A	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/14747	International filing date (day/month/year) 22.12.2003	Priority date (day/month/year) 23.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D493/04		
Applicant NOVARTIS AG et al.		

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 5 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  30.06.2004	Date of completion of this report  14.03.2005
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer  Steendijk, M  Telephone No. +49 89 2399-8460 

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/EP 03/14747**

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-39 as originally filed

**Claims, Numbers**

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 8,10,14-16

because:

☒ the said international application, or the said claims Nos. 8,10 relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 14-16

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)

Yes: Claims 1-13

No: Claims

Inventive step (IS)

Yes: Claims

No: Claims 1-13

Industrial applicability (IA)

Yes: Claims 1-7,8,11-13

No: Claims

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/14747

- 1) The present application relates to C4-desmethyl-epothilone derivatives, their preparation and intermediates specific for preparing C4-desmethyl-epothilone derivatives (III and IV) (claims 1-13), an intermediate of formula II (claim 14) and a method for isolating C4-desmethyl-epothilone B (claims 15-16).

The subject-matter of claims 14-16 was not searched following an objection of non-unity and failure of payment of further search fees. This subject-matter is therefore not further considered in the preliminary examination.

2) Cited documents

- D1: WO 99/65913 A  
D2: JOURNAL OF NATURAL PRODUCTS, 2001, vol. 64, no. 7, pages 847-856,  
D3: WO 98/25929 A  
D4: ANGEWANDTE CHEMIE. INT., 1998, vol. 37, no. 15, pages 2014-2045,  
D5: JP 03 048641 A (PAJ-abstract)  
D6: ANGEWANDTE CHEMIE INT., 1997, vol. 36, no. 19, pages 2093-2096, ISSN:  
D7: WO 03/022844 A

Document D7 was published after the priority date. The priority seems not valid in as far as compounds in which R3 represents hydrogen are concerned.  
With respect to such subject-matter, D7 would represent additional prior art.

3) Novelty

Documents D1 and D2 already describe C4-desmethyl-epothilones (see compounds 5, 6, 16-19, 28-29 and 33-35. The compounds of D1/D2 have been excluded by proviso's.

Documents D3 and D4 describe epothilone derivatives and various preparation strategies, not however specifically C4-desmethyl derivatives. With respect to D3 the C4-desmethyl derivatives can be considered a new selection.

Document D5 describes the structurally closest known compounds with respect to the intermediate of claim 12; D5 describes esters instead of the free acid.

Document D6 discusses preliminary SAR-studies on epothilone-derivatives from which the C1-C8-sector seemed rather intolerant to modification.

It is observed that document D7 specifically mentions 4-desmethyl Analogues (see

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page 45); D7 does not specifically describe compounds of the present application in which R3 represents hydrogen and for which the priority may not be valid.

4) Inventive step

Merely as alternatives to the compounds of D1 and D2 the claimed matter would seem obvious to the person skilled in the art, in particular in view of document D3 from which the claimed matter can be considered selected.

In this context it is observed that document D6 cannot be cited to substantiate any prejudice against C4-desmethyl-epothilones at the time of filing of the present application.

Indeed D6 mentions relative intolerance to modification in the C1-C8 region. However the C4 position is not specifically mentioned in D6, whereas from the later published D1 and D2 it was known that this position may indeed be modified with preservation of activity.

This observations is further confirmed by document D7, which is considered as prior art in as far as the priority would not be valid.

Independently from the objection above, the intermediates of claims 12 and 13 are not considered to involve an inventive step. These intermediates include the relevant intermediates orientated towards the known desmethyl compounds of D1/D2. Merely as solution to the problem of providing suitable intermediates for a synthetic route towards these known compounds no inventive step is recognized as this route was already known for the analogue preparation of C4-dimethyl derivatives (see D3, fig. 13 and D4, page 2026).

5) Further observations

The term "lower" for chain lengths has no defined meaning and therefore renders the claims unclear.

Claims 8 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).